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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,229	11/17/2003	Tariq M. Rana	UMY-041RCE2	5733

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EXAMINER	
CHONG, KIMBERLY	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,229	RANA, TARIQ M.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-34* is/are pending in the application.

4a) Of the above claim(s) *18-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10/01/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 04/01/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 04/01/2009, claims 2-34 are pending in the application. Claims 2-17 are currently under examination.

Response to Applicant's Arguments

Re: Claim Objections - maintained

Applicant has not responded to the claim rejection and therefore claims 15-17 remain objected to because of the following informalities: Claim 15 recites the limitation "the siRNAi" and it appears to have misspelled "siRNA". Claims 16 and 17 are objected to because they depend from claim 15. Appropriate correction is required.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 2-8 and 10-17 under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722 of record cited on PTO Form

892 filed 04/02/2007), ten Asbroek et al. (Nucleic Acids Research 2000, Vol. 28: 1133-1138), Hojo et al. (Eur Respir J, 1998 of record cited on PTO Form 892 filed 04/02/2007), Hammond et al. (Nature Reviews Genetics, 2001 of record cited on PTO Form 892 filed 04/02/2007), Bass et al (Nature, 2001 of record cited on PTO Form 892 filed 04/02/2007) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005) is maintained for the reasons of record.

Applicant's arguments filed 10/01/2009 have been fully considered but they are not persuasive. Applicant argues Ecker fail to teach or suggest siRNA capable of single nucleotide discrimination wherein the antisense comprising a 5-bromo-uridine or 5-iodo-uridine positioned opposite a point mutation and Ecker fail to fail to teach a 2,6-diaminopurine positioned opposite a point mutation. Ecker reiterates their argument that teachings of Ecker et al. are directed to antisense DNA oligonucleotides and teach away from the claimed invention because Ecker teach that RNase H cleaves the RNA strand and DNA antisense is the preferred molecule for inhibition of gene expression.

In response to Applicant's arguments, Ecker was not relied upon for teaching siRNA molecules. Ecker was relied upon for the fact that it was known in the art the desire to target mutant alleles and it was known in the art to make an inhibitory nucleic acid molecule wherein the complementary strand comprise a modified nucleotide opposite the point mutation stabilizes the hybridization of the inhibitory molecule to the target. As acknowledged by Applicant, Ecker et al. teach incorporation of a 2, 6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated

gene. Given that a thymine is the equivalent of a uracil in a DNA strand, when targeting DNA one of skill in the art would clearly incorporate this modified base opposite a mutated thymine. One of skill in the art would have been motivated to substitute the antisense compound taught by Ecker et al. with a more efficient inhibitory molecule for the sole purpose of targeting a mutant gene more efficiently and silencing gene expression of said mutant target gene more efficiently given all that was known in the art at the time of the invention about siRNA being more efficient at silencing gene expression. Moreover, given that both the antisense compound and siRNA compound are designed to recognize a target gene through complementarity to the target gene, of skill in the art would be motivated to design an siRNA to a mutant target gene and have a reasonable expectation of success at being able to initiate gene silencing of a mutant target gene using a siRNA.

Applicant's argue ten Asbroek et al. and Hojo et al. fail to make up for the deficiencies of Ecker et al. because the references do not teach or suggest any RNA oligonucleotide or a siRNA molecule. Applicant argues both Hammond et al. and Bass et al. fail to make up for the deficiencies of Ecker because the do not suggest siRNAs comprising any modified nucleotides . Applicants further argue Tuschl et al. do not teach the structure and function of the claimed siRNA and fails to suggest the specific positioning of a modified base in the antisense strand or that siRNAs can be used for single nucleotide discrimination and argue that Tuschl et al. teach away from the claimed invention because Tuschl et al. states the nucleotides in the center of the

siRNA opposite the cleavage site are important specificity determinants and should not be modified.

In response ten Asbroek et al., like Ecker et al. was relied upon to teach how well known it was in the art to target mutant alleles using inhibitory nucleic acid molecules. Hojo et al. was relied upon to teach the obviousness of targeting a mutant cancer gene wherein the mutation responsible for mediating the disease is found on an adenine or thymine. Thus because it was well known at the time of filing of the instant invention regarding the desirability to target a mutant allele in a pair of alleles wherein the mutant allele is responsible for the progression of certain diseases, such as cancer and because siRNAs were emerging as the new preferred class of inhibitory molecules to silence gene expression, it would have been obvious to make siRNA to target mutant alleles.

Applicant's arguments regarding Tuschl et al. are not persuasive. First, the claims recite the modified base is located at an internal residue of the antisense strand of the siRNA however the claims do not recite a specific location on the strand and the specification does not define which specific nucleotides on the antisense strand are considered internal. Therefore an "internal residue" could mean any nucleotide on the strand except for the 5' or 3' end nucleotide. Tuschl et al. only mentions the nucleotides opposite the cleavage site, which are usually nucleotides 10-12 from the 5' end and therefore one of skill in the art would read from Tuschl et al. that any other nucleotide opposite a mutant allele could be modified and therefore Tuschl et al. does not teach away from modifications of internal nucleotides. Tuschl et al. teach the

development of siRNA as a new alternative to antisense technology and therefore one would have wanted to use this new technology which was proven to be more sequence specific and would have had a reasonable expectation of success at making a siRNA targeted to a mutant allele. Moreover contrary to Applicant's assertion, Tuschl et al. teach siRNA duplexes can discriminate between mutant or polymorphic alleles which are important in therapeutic developments involving said mutant alleles (see page 50).

Applicant argues the skilled artisan at the time of the invention would not have had a reasonable expectation of success because antisense and siRNA operate through very different mechanisms. Applicants argue that although the Xu et al. reference does in fact point to evidence at the time of filing of the instant invention one of skill in the art would have had a reasonable expectation of success at generating a molecule targeted to a mutant allele because many other references question the skilled artisans motivation and reasonable expectation of success at generating a siRNA that was capable of single nucleotide specificity.

In response, the teachings of the prior art provide a sufficient basis for a reasonable expectation of success. Obviousness does not require absolute predictability. Given that the prior art taught a reason to target mutant alleles using an inhibitory nucleic acid molecule such as antisense and given that Tuschl et al. found that siRNA with a single mismatch did not mediate RNAi and given that Xu et al. demonstrates what Tuschl et al. found i.e. siRNA capable of single nucleotide discrimination, one of ordinary skill in the art would have had a reasonable expectation of success.

Applicant points to numerous references which purport to demonstrate why one skilled in the art would not have had a reasonable expectation of success. Applicant's point to examples of each of the references wherein the siRNA with a single nucleotide mismatch was capable of mediating RNAi to similar levels as compared to siRNA with perfect complementarity to the target. The claims are not drawn to incorporation of single nucleotide mismatch in a strand of siRNA, the claims are drawn to incorporation of a modified base in the antisense strand which enhances the binding interaction between the siRNA and the target. This has been demonstrated by Ecker et al. using antisense technology as argued in the previous rejection of record and above. Furthermore, Tuschl et al. does recognize that altering a nucleotide in the antisense strand of a siRNA reduced the ability of that siRNA to mediate RNAi and recognized that this fact could be beneficial to allele-specific targeting and this was demonstrated by Xu et al.

Boutla et al. does not provide evidence that single nucleotide discrimination were beyond the limits of siRNA technology as alleged by Applicant. As stated previously, while Boutla et al. demonstrates siRNA with single nucleotide mismatches were still capable of inducing RNAi in whole organism, introduction of the single nucleotide mismatches did not silence the gene as efficiently as with no mismatches and Boutla et al. states that this observation will require a more detailed analysis to access at what position and to what degree sequence deviations can or cannot be tolerated (see page 1779). Thus, one of ordinary skill in the art would be motivated to

make a siRNA to investigate whether said molecule could be used as a therapeutic for targeting mutant alleles.

Applicants cite Holen et al. as evidence of a lack of reasonable expectation of success. Holen et al. on page 1763 recognizes that low or no tolerance for mismatched would make siRNAs a valuable tool for allele-specific degradation of the aberrant mRNA in various dominant negative disorders resulting from single base pair mutations and did find molecules with a single mismatch reduced the effect of siRNA moderately and double mismatches had almost no activity. In reading the entire discussion of this level of tolerance Holen et al. attributes the activity of some of the siRNA mutants with mismatches to the target to in vitro and in vivo systems (see page 1763 second column). Thus, Holen et al. do not lead one of ordinary skill in the art to believe that single nucleotide discrimination with siRNA is unachievable.

Applicants cite Yu et al. as evidence of a lack of reasonable expectation of success and point to page 6048 and Figure 2c. Yu et al. makes no mention of incorporation of mismatches or modified bases for single nucleotide discrimination to target mutant alleles. The experiment pointed to by Applicant was designed to incorporate mismatches in to the siRNA to determine if the siRNA would target RNA but not its complement and Yu et al. found that the ability of the hairpin siRNA to inhibit the complementary strand with a mismatched sequence was reduced. This would therefore indicate siRNAs were in fact capable of single nucleotide discrimination (see page 6049).

Applicant points to Hamada et al. as additional support for a lack of a reasonable expectation of success. The Hamada et al. reference has not been make of record and Exhibit B has not been filed along with the last response 10/01/2009. However, based on Applicant's summary of the results of Hamada et al., the fact that Hamada et al. found that the single-nucleotide mutant siRNA showed a significant decrease in mediating RNAi as compared to the wild-type siRNA does not do not lead one of ordinary skill in the art to believe that single nucleotide discrimination with siRNA is unachievable. In fact, it would provide motivation for one of ordinary skill in the art to further pursue this observation in efforts of generating siRNA to target mutant alleles.

Therefore, as stated previously it was well known at the time of filing of the instant invention regarding the desirability to target a mutant allele in a pair of alleles wherein the mutant allele is responsible for the progression of certain diseases, such as cancer and in do so provides a promising therapeutic approach to treating certain diseases and because siRNAs were emerging as the new preferred class of inhibitory molecules to silence gene expression, it would have been obvious to make siRNA to target mutant alleles

The rejection of claims 2-17 under 35 U.S.C. 103(a) as being unpatentable over Klug et al. (European Journal of Physiology 2001, cited on IDS filed 11/20/2007), Ecker et al. (US Patent No. 5,965,722 of record cited on PTO Form 892 filed 04/02/2007), Hammond et al. (Nature Review Genetics, 2001 of record cited on PTO Form 892 filed 04/02/2007), Bass et al (Nature, 2001 of record cited on PTO Form 892 filed

04/02/2007) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005) is maintained for the reasons of record.

Applicant's arguments filed 10/01/2009 have been fully considered but they are not persuasive. Applicant argues Klug et al. fail to teach or suggest siRNA capable of single nucleotide discrimination and nothing in the art suggests a need for an alternate molecule. Further Applicant argues even if one of ordinary skill in the art would have been motivated to use a siRNA, there would not have been a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to substitute the antisense compound taught by Klug and Ecker et al. with a more efficient inhibitory molecule for the sole purpose of targeting a mutant gene more efficiently and silencing gene expression of said mutant target gene more efficiently given all that was known in the art at the time of the invention about siRNA being more efficient at silencing gene expression. Moreover, given that both the antisense compound and siRNA compound are designed to recognize a target gene through complementarity to the target gene, of skill in the art would be motivated to design an siRNA to a mutant target gene and have a reasonable expectation of success at being able to initiate gene silencing of a mutant target gene using a siRNA for the reasons stated above.

Thus the rejection of record is maintained.

The rejection of claims 2-17 under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (cited on PTO Form 892 filed 11/15/2005) and Ecker et al. (US Patent No. 5,965,722 of record cited on PTO Form 892 filed 04/02/2007) is withdrawn as Applicant has provided a statement that the Xu et al. applicant and the instant application were commonly owned at the time of the instant invention.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Tracy Vivlemore at 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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